EXHIBIT H

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/981,664	10/30/2007	William J. Boyle	06843.0049-01000	9620

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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
02/05/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/981,664	BOYLE ET AL.	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-91* is/are pending in the application.

4a) Of the above claim(s) *54-91* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30,31 and 33-53* is/are rejected.

7)☒ Claim(s) *32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/3/08, 10/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response received December 2, 2009 is acknowledged.

Claims 1-29 have been canceled.

Claims 30-91 are pending.

Applicant's election of group I, claims 30-53 as they read on nucleic acids, and the species of the CDRs of SEQ ID NOs:13 and 14 as an encoded antibody structure in the reply filed on December 2, 2009 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 54-91 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 2, 2009 as explained above.

Claims 30-53 are under examination in this office action.

Information Disclosure Statement

2. The IDS forms received 7/3/08 and 10/8/08 are acknowledged and have been considered.

Specification

3. The specification and abstract are objected to because they do not discuss the instant claimed subject matter, i.e. polynucleotides. Appropriate amendment to make the title and abstract more commensurate in scope with that which has been claimed is suggested. Applicant is also requested to update the priority information present in the

instant application, as well as update the status of any applications discussed within the text of specification as originally filed.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 30, 31, and 33-53 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotide compositions encoding antibodies which bind OPGL wherein the encoded antibody comprises a) the 3 CDRs of SEQ ID NO:13 and the 3 CDRs of SEQ ID NO:14, b) the entire V_H sequence of SEQ ID NO:13 and any V_L, c) the entire V_L sequence of SEQ ID NO:14 and any V_H, d) the entirety of SEQ ID NOs:13 and 14, or e) any of the aforementioned scenarios when SEQ ID NO:13 is substituted with SEQ ID NO:2 and/or SEQ ID NO:14 is substituted with SEQ ID NO:4, does not reasonably provide enablement for more. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant has broadly claimed compositions comprising nucleic acids which encode antibodies which bind human OPGL. The specification discloses that applicant made an exemplary antibody named αOPGL-1, which when sequenced yielded the complete heavy chain of SEQ ID NO:2 and light chain of SEQ ID NO:4. It is further disclosed that SEQ ID NO:13 is the variable heavy (V_H) domain of αOPGL-1 (and thus it is a truncation of SEQ ID NO:2) while SEQ ID NO:14 is the V_L of said antibody. αOPGL-1 was made by immunizing a transgenic mouse comprising the human Ig locus, and thus the resulting antibody is a fully human antibody. The breadth of the claims read not only upon nucleic acids encoding αOPGL-1 itself, but upon nucleic acids which encode mutants of αOPGL-1 wherein the identity and position of such mutations within the structure of the working example αOPGL-1 antibody are unspecified.

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

It is also known in the art that very different V_H chains (about 50% homologous) can combine with the same $V\kappa$ chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different $V\kappa$ sequences to produce antibodies with very similar properties. These results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (FUNDAMENTAL IMMUNOLOGY, William E. Paul, M.D. ed., 3d ed. 1993, page 242). It is also known that given one specified variable domain, either heavy or light, that skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano et al., see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain (heavy or light) is used in the screening assay.

Since all CDRs contribute to binding, and binding can be disrupted in unpredictable ways due to mutations as small as a single point mutation, applicant's recited genus of antibodies encompassing mutations within the CDRs, as is shown in

claims 50-53 which recite percent identity, as well as claim 30 which minimally only requires 1 CDR of a V_H and 1 CDR of a V_L do not reasonably appear to be enabled. Note that while it would be very easy for an artisan to make mutations to arrive at the 95% (or 99%) identity limitation, it is known in the art that mutations unpredictably influence binding as per Rudikoff et al. Note that even a recitation of 100% identity for all 3 CDRs of a variable domain (either V_H or V_L) would not allow a skilled artisan to make the instant claimed invention because a complete variable domain is required for use in screening assays that would identify suitable binding pairs that maintain antigen specificity. Note that this is also why claims such as 33 and 34 have been rejected. For example, claim 33 recites "…comprising *an* amino acid sequence of SEQ ID NO:13." The use of the indefinite article "an" rather than the definite article "the" means that the true scope of the claim reads on not only the full length sequence of SEQ ID NO:13, but on truncations of undefined size as well. In the absence of any definition in the specification, such a truncation comprising "an amino acid sequence" is as small as two consecutive residues. Amending such claims to recite the definite article would likely be beneficial in obviating this issue which is present in multiple claims of the instant application.

Therefore, based upon the breadth of the claimed invention, the teachings of the art, and the lack of guidance and direction disclosed in the specification, a skilled artisan would be unable to make and use the full breadth of the claimed genus of antibodies without first performing additional, unpredictable research.

6. Claims 30, 31, and 33-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant has broadly claimed compositions comprising polynucleotides which encode antibodies that bind human OPGL. The encoded antibody is recited as comprising numerous distinct partial structures. The specification disclosed that the

complete heavy and light chain sequences of the αOPGL-1 antibody of the working examples are SEQ ID NOs:2 and 4 respectively, with the complete V_H and V_L subsequences being SEQ ID NOs:13 and 14 respectively. From this information, applicant has claimed encoded antibodies with only one CDR of each chain specified, encoded antibodies wherein the specified structure is reasonably even less than a complete CDR due to the recitation of "...an amino acid sequence of..." which allows for sequence as small as two residues from anywhere within the indicated sequence to be present, and encoded antibodies comprising mutations at unspecified positions due to percent identity language.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412) 19 F. 3d 1559, the court stated: "A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin [e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the

absence of knowledge as to what that material consists of, is not a description of that material."

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

It is well established in the art that the formation of an intact antigen-binding site requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three different complementarity determining regions, CDR1, 2 and 3, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin (Janeway et al., see entire selection). It is also known that single amino acid changes in a CDR can abrogate the antigen binding function of an antibody (Rudikoff et al., see entire document, particularly the abstract and the middle of the left column of page 1982).

It is also known in the art that very different V_H chains (about 50% homologous) can combine with the same $V\kappa$ chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different $V\kappa$ sequences to produce antibodies with very similar properties. These results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics (FUNDAMENTAL IMMUNOLOGY, William E. Paul, M.D. ed., 3d ed. 1993, page 242). It is also known that given one specified variable domain, either heavy or light, that skilled artisans can screen libraries to identify other variable domains that will pair with the starting variable domain and maintain antigen specificity (Portolano

et al., see entire document, particularly figure 1). Thus, it is known in the art that artisans can screen for other variable domains that will ensure a functional antibody of defined antigen specificity if a full variable domain (heavy or light) is used in the screening assay.

Since all CDRs contribute to binding, and binding can be disrupted in unpredictable ways due to mutations as small as a single point mutation, applicant's recited genus of antibodies wherein one or more (up to all six) CDRs are mutated due to the recitation of "at least 95% (or 99%) identity" does not provide a reasonable correlation between structure of the recited antibody and the functions of binding OPGL. Note that the specification does not provide data that a single CDR in isolation binds OPGL, and thus more structure than this is needed to satisfy the recited functional limitation. Further, the instant claims appear to allow an artisan to pick and choose from among multiple combinations of partial structures in generating the encoded antibody. However, the specification does not disclose the structures that need to be present along with any one given CDR to satisfy the functional requirement of binding. For example, as discussed above, it is known in the art that possession of a complete V_H (or V_L) allows for screening to occur to obtain the missing variable domain. The instant claims read upon situations wherein one variable domain is completely defined and the other variable domain comprises, for sake of example, one CDR. The specification does not provide information on how and with what other sequences and structures the CDR is to be joined (other than in the form of the complete variable domain from which it was isolated) such that the functional limitation of binding is preserved. Additionally, the structure that must be maintained by truncations comprising at least two consecutive amino acids of the recited sequences which maintain antigen binding also does not appear to be disclosed.

Therefore, it appears that applicant's recited genus polynucleotide compositions encoding antibodies which bind OPGL lacks adequate written description because the breadth of the claimed genus is not supported by either a representative number of examples covering the breadth of the claimed subject matter or a disclosure of what positions within the recited CDRs can or cannot be changed while maintaining the

recited functional properties of said genus. As such a skilled artisan would reasonably conclude that applicant was not in possession of the recited genus of polynucleotides, and thus was also not in possession of vectors, host cells, and methods of using host cells to make polypeptides which utilize said polynucleotides.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 30, 33, 34, 36-42 and 44-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (US 6017,729, of record) in view of Queen et al. (US 5,693,762).

Anderson et al. disclose monoclonal antibodies which bind RANK (see entire document, particularly Example 3). These antibodies were made by standard murine hybridoma technology. The use of such antibodies for in vivo diagnostic and therapeutic applications is disclosed (see particularly columns 10 and 11). Note that RANK is another name in the art for OPGL. These teachings differ from the claimed invention in that they do not disclose sequence information for their antibodies.

Queen et al. disclose that it is advantageous to humanize murine antibodies that are to be administered to humans for diagnostic or therapeutic methods to reduce immunogenicity and decrease the potential for eliciting a HAMA response which would neutralize the administered antibody (see entire document). They further disclose that humanized antibodies can be expressed as various fragments, such as single chain and Fab constructs (see particularly column 17). The nucleic acids encoding the starting murine antibody must be obtained before the humanization process begins, which essentially takes the 6 CDRs of the murine (could actually be any animal) parent antibody and places said CDRs into human frameworks with or without human constant domains as is desired to yield the humanized antibody. Given the recombinant nature of the work, polynucleotides, vectors, host cells, and the expression of antibodies from host cells transfected with nucleic acid constructs are all disclosed.

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to humanize the antibodies of Anderson et al. so that they would be less immunogenic when administered as part of the methods of use taught by Anderson et al. The ordinary artisan would have a more than reasonable expectation of success in doing so given the numerous working examples concerning humanizing different starting antibodies that are disclosed by Queen et al. It should be noted that SEQ ID NOs:2, 4, 13, and 14 were obtained from an antibody made in a transgenic mouse expressing the human Ig locus. Thus these sequences are reasonably considered to be human. The process of humanization places heterologous CDRs into human frameworks and constant domains. The instant claims recite "...encodes *an* amino acid sequence of SEQ ID ...". As has been discussed in other rejections, such a recitation reads on the required sequence being only two consecutive amino acids in length. Given that the vast majority of the humanized antibody sequence is of human origin, humanizing the antibodies of Anderson et al. would reasonably yield antibodies comprising at least two consecutive amino acids that are also present in the recited SEQ ID numbers. Amendment of the claims to recite "...encodes *the* amino acid sequence of SEQ ID ..." would no longer allow the claims to encompass truncations of the recited SEQ ID numbers and would obviate this rejection.

Claim Objections

9. Claim 32 is objected to as being dependent upon a rejected independent claim, but would be allowable if rewritten in independent form including all of the limitations of the independent claim and any intervening claims.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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